THE VIRTUES AND VICES OF SULPHAPYRIDINE

A Critical Survey

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"We have here a group of drugs (i.e. the sulphanilamide group) which has offered marvellous healing powers . . . however, which possesses a definite, yet poorly understood, power to harm patient as well as organism. . . . Considerable care and control in the handling and administration of these drugs is clearly necessary" (Mayer).¹

Domagk's demonstration, in 1935, of a new azo-dye, called prontosil rubrum, which possessed highly protective powers in the case of experimental streptococcal infections in animals, opened up a great vista of chemotherapeutic agents, the end of which we cannot begin to foresee as yet.

In 1938, Whitby showed that a pyridine derivative of sulphanilamide was active in relatively small doses against pneumococci of Types I, II, III, V, VII, VIII in experimental infections in mice—especially types I, VII and VIII, and that it was active also against the haemolytic streptococcus and the meningococcus.

It was shown by Whitby and McIntosh, that sulphapyridine *per se* did not produce a leucocytosis, or an increase in the opsonin reactions, or in the formation of specific antibodies when mice were fed on this drug alone. Therefore, the drug must exert its influence on the bacteria quite independently of the immunity of the body. Fleming² showed that this action, however, was enhanced by the presence of a specific immune serum. Thus, it appears that the drug must act, not as a simple germicidal, but, by neutralising some metabolic or enzymatic function of the bacteria themselves.

The effective dose of the drug is proportional to its absorption, which, in its turn, is proportional to the method of administration.

The *oral route* has its maximum absorption when the drug is given crushed, and dissolved in a large quantity of water, on an empty stomach, with no constipation. Other methods of administration per oris are progressively less effective.

The *intramuscular route* is probably the one designed for total maximum absorption, and its only real drawback is the necessity of repeated injections into an ill patient—a factor not to be overlooked in any form of medication.

The *intravenous route*, using a diluted solution of the sodium salt, is certain and rapid, but, because of its extreme alkalinity (pH 11), it is liable to cause severe vasomotor and respiratory depression (Nelson, 1941).³

The *intrathecal route*, especially of value in the treatment of meningitis, again using a diluted solution, is the subject of some controversy, but, because of Fleming's findings regarding the increased efficacy of the drug when used with an immune serum, it appears better not to use this route for sulphapyridine but to leave the way open for its utilization by the specific immune serum.

Whichever method is used, once absorbed, the drug circulates in the blood, partly as free sulphapyridine, and partly as acetylated-sulphapyridine—the latter being quite inactive. The proportion of these constituents varies greatly from case to case, and it is not known as to what factor or factors this is due.

Excretion of both fractions is performed solely by the kidney. This has a great significance (vide infra).

Before considering the therapeutic application of sulphapyridine, it would be well to consider, briefly, some of the more common *toxic manifestations* as shown in the following table taken from Long's Summary:⁴

TOXIC MANIFESTATIONS

<i>Toxic Manifestation</i>	<i>Incidence</i>	<i>Time of Appearance</i>
Nausea and vomiting	Very frequent	Early (do not give Sod. Bic.)
Dizziness	Common	Early
Cyanosis	Faint, common	Early
Fever	Uncommon	5-9th days usually: may be 1-21st
Rash	Uncommon	5-9th days usually: may be 1-30th
Hepatitis	Rare	Early or late
Haematuria	Common	1-10 days
Anuria with azotaemia ..	Not uncommon	2-14 days. (B.P. & fundi normal)
Acute leukopenia with granulocytopenia	Common especially children	1-10 days (give Vit. C)
Agranulocytic angina ..	Uncommon	14-25th days
Hyper-leucocytosis ..	In presence of haemolytic anaemia	14-40th days
Mild haemolytic anaemia ..	Common	Early and late
Acute haemolytic anaemia ..	Uncommon	1-5 days

This is a formidable list of diseases to be caused by a mere physician! But these diseases should not be dismissed lightly; four examples of these toxic manifestations have been chosen from the literature to illustrate very briefly the serious disasters that may occur. (For full description, read the references.)

1.—**Fatal Agranulocytosis** after sulphapyridine.⁵—A young woman was admitted to hospital with a severe microcytic anaemia, and sore throat with temperature—she was treated with sulphapyridine, and, although there was some improvement of the infection, she gradually relapsed, the anaemia progressed, and she died after a four weeks' illness, during which time she had received 75 grammes of sulphapyridine. The only finding at autopsy was multiple small patches of fatty degeneration in the liver.

2.—**Fatal Anuria** after sulphapyridine in pneumonia.⁶—Male, aged 35, with pneumonia; in all he received 10 grammes of the drug, yet, within 24 hours, he had pain in the lumbar region, with heavily blood-stained urine—two days later the urine contained a heavy crystalline deposit of acetyl-sulphapyridine. The blood urea went up to 155 mg. %. Decapsulation of the kidneys was tried but death ensued.

3.—**Cerebral symptoms** occurring with sulphapyridine⁷ therapy. In a series of five cases, two deaths occurred. There was persistence of cerebral symptoms, in spite of intensive treatment. There was a gradual return of the C.S.F. to normal, and yet the patient's symptoms became, either progressively severe, or returned after transient improvement.

4.—**Severe skin reactions.**⁸—Out of 87 cases of gonococcal urethritis, three developed severe exfoliative dermatitis.

Consideration of these brief reports leads us to the conclusion that sulphapyridine is an extremely potent drug; further it appears that when an organ of the body has its function grossly deranged by some other disease process, it may not be able to withstand the assault of such extra toxicity.

The **therapeutic applications** of sulphapyridine can now be considered:—

A. Respiratory system

(1) *Lobar Pneumonia*.—It is in this disease that sulphapyridine has gained its full reputation; and deservedly so. But there are certain reservations to be made:

(a) In the typical lobar pneumonia in a young healthy adult it is probable that, given certain diagnosis and good nursing, aspirin could take the place of sulphapyridine; furthermore if the case was not responding too well, the giving of a specific anti-serum against the particular type of organism is not only sound but scientific in its application; coupled with this fact one is reminded of Fleming's findings on the value of immune serum and sulphapyridine when used together.

(b) It is becoming more evident that following the use of sulphapyridine the post-pneumonic morbidity rate is greater in such cases; e.g. instead of finding thick pus in a post-pneumonic empyema with its attendant adhesions, one often finds a pale thin fluid without adhesion formation which prevents effective drainage being undertaken; or, there is delayed resolution in the pneumonic lung.

(2) *Other forms of "pneumonia."*—Typical lobar pneumonia is definitely becoming less frequent nowadays and many atypical forms are seen. In these cases sulphapyridine has a definite part to play, provided persistent use of the drug is not allowed because of temperature or cough. If the drug is going to be of value, it will have done its work during the first five days if given in adequate doses.

(3) *Upper Respiratory Tract*.—e.g. common colds and sore throats.—There is no evidence of specificity in these diseases and sulphapyridine should *not* be given expectantly.

(4) *Otitis Media*.—Its use is of great value especially in the early stages.

B. Nervous System

In meningococcal, pneumococcal and gonococcal meningitis, the use of sulphapyridine is definitely indicated; but there is the risk of overdosage with most unfortunate results (vide supra). Therefore, dosage must be controlled by the amount of pus in the C.S.F. as shown by repeated lumbar puncture. That sulphapyridine is not infallible, the following case will show:

Case 1.—A.M. aet. 28—History of bilateral chronic discharging ears since 12. When first seen there was a history of decreasing mental capacity with some vomiting, during the past four days; and earache in left ear. O.E. Temp. 102.4 and pulse 56. Positive Kernig's sign, neck rigidity. No papilloedema. There was no discharge from the ear. Lumbar puncture showed fluid under pressure, which was opalescent. Microscopically pneumococci were present and there were 400 cells per c.c., nearly all polymorphs. In view of vomiting, and pulse rate together, and with history of ear trouble, the diagnosis of pneumococcal meningitis, secondary to cerebral abscess, from the ear, was made. The left ear was explored the next day: some bulging of the dura, but no pus was found. During this time a total of sulphapyridine grammes 15 was given. On the fourth day the C.S.F. appeared more normal and as the patient was vomiting a great deal, the sulphapyridine was stopped. Three days later there was some papilloedema and nystagmus was present; coarse to right, and fine to left. In view of these findings, a second exploratory operation was performed, with no result. All the time his temperature was swinging between 99.4° in morning to 101.4° at night. Gradually the temperature mounted higher and a further course of sulphapyridine was tried (about 20 grammes). The patient began to have rigors, and, after one month's illness he died. At autopsy, in spite of the most intensive search, the only finding was of basal pneumococcal meningitis.

It is interesting to note that there was a persistence of the basal meningitis with a more or less normal C.S.F. towards the latter half of the illness. This is why serum was not used.

C. Urinary System

(1) *Pyelitis and Cystitis*.—There is no doubt that sulphapyridine is of great value in treating these infections, provided the urine is kept alkaline.

(2) *Gonococcal infection*.—Sulphapyridine is most efficacious in the treatment of gonorrhoea in both male and female. The drug can be used in gonococcal meningitis and in other gonococcal manifestations.

Case 2.—Mrs. X. aet 59; husband has old gonococcal stricture. She complained of a sudden pain in the left elbow which became swollen and tender; and she had temperature, 100°. The surrounding tissues appeared thickened and there was an effusion into the joint. This was aspirated and gonococci were found in the fluid. The immediate exhibition of sulphapyridine plus immobilisation of the part, in plaster of Paris, caused complete subsidence in 10 days, and, now there is a perfect result.

D. Alimentary System

(1) *Peritonitis*.—General or local. It has been found of no value in this type of infection.

(2) *Pneumococcal peritonitis*.—This is one of the major indications for its use. Because the patients are nearly all children, fluid intake must be kept up and in order to prevent agranulocytosis and leukopenia, Vitamin C must be given at the same time.

Case 3.—J. C. aet. 4½—of good and intelligent family—felt slight “tummy-ache” at 11.45 a.m. By 12.30 p.m. she felt sick, but insisted on eating a good lunch. She was put to bed and became flushed. Her mother palpated her abdomen, and, thought she felt some rigidity whilst the child slept. At 4 p.m. the temperature was 99° and the pulse 96, and there was some central abdominal pain. The abdomen felt relaxed, but the patient seemed rather flushed and bright-eyed. At 6 p.m. the pulse was 104 and there appeared to be rigidity in the R.I.F. By 8 p.m. the pulse was 112 but temperature only 99.8°. In view of these findings it was decided to operate on the child at midnight and anaesthesia was induced with paraldehyde p.r. followed by gas and oxygen. The abdomen was opened over the appendix area—this organ was normal, but there was a thin turbid fluid inside the abdomen, which microscopically showed pneumococci. She was given in all grammes 11 of sulphapyridine, and although she became very toxic, this improved on stopping the drug, and she made an uninterrupted recovery. She was also given vitamin C.

(3) *The Dysenteries*.—Sulphapyridine has a definite place in their treatment, especially when the disease has entered into a subacute or chronic stage, and especially in the Sonne type.

Case 4.—R. P. aet 20. She stayed on a farm during the very hot summer, and drank much water and returned home with a high temperature and diarrhoea. The diarrhoea persisted and a culture showed the Sonne dysentery bacillus to be present. After three weeks of diarrhoea of varying degrees, she was given a total of sulphapyridine grammes 20 over four days. The diarrhoea stopped, and although her colon is irritable to certain things such as iron, she has made a good recovery. It was afterwards proved that the water drunk was infected and that there was a mild outbreak in that district.

E. Cardiovascular System

Sulphapyridine has been tried in subacute bacterial endocarditis but without success.

The **dosage of sulphapyridine** is governed by the necessity of bringing the blood concentration of the drug to its optimum concentration (10 mgs. %) as soon as possible, and, of keeping it there. Therefore, for an adult the usual dose is 2 grammes (4 Tablets), repeated in four hours, and then 1 gramme every four hours for 60 hours, and thereafter 0.5 gramme every four hours as long as necessary.—In this way the effective blood concentration is kept up.

For children the initial dose is 0.5 gramme—1 gramme followed by the maintenance doses as shown in the table.

Age	1-3 months	6-12 months	2-3 years	5 years
Dose in Tablets	½ Tablet 4 hourly	½ Tablet 4 hourly	1 Tablet 6 hourly	1 Tablet 4 hourly

In pneumococcal meningitis an even higher initial dose is recommended (Hodes, Gimbel & Burnett): for example, 1-3 grammes by mouth or nasal tube for young infants, and 6 to 12 grammes for older children or adults.

Whatever the dosage, *the fluid intake is most important*. It must be adequate, not only for the normal requirements of the body (1500 c.c. per day) but allowance must be made for *fluid loss by temperature, etc.*; and especially in children, with their higher basal metabolism, the fluid intake must be greater pro rata. This must be strictly enforced.

Antopol⁹ showed that, even with a single large dose of sulphapyridine there was a great danger of causing massive precipitation of free sulphapyridine in the nephrons and so causing great damage to the kidneys. Excess of fluid will help to guard against this danger.

Much stress has been laid upon the toxic manifestations of sulphapyridine—indeed, undue prominence has been given to them in this survey. This has been done deliberately because, firstly, they do constitute a very definite danger; and secondly, only by careful analysis of the results can the subject of chemotherapy be pushed further forward. To give undue praise because of one's enthusiasm for any new drug is to do great disservice to the cause of human suffering. Therefore, let us keep a more balanced view, for, surely, sulphapyridine is only one of the pioneers of its race.

CONCLUSIONS

Deduction from the above show that the following inflammatory conditions should be given immediate sulphapyridine therapy, viz. pneumococcal peritonitis; all acute and chronic gonococcal infections; acute pyelitis and cystitis. otitis media; and acute meningitis of meningo-pneumo- and gonococcal origin. There is an optimum time both for its use, i.e. as soon as the diagnosis has been confirmed, and, its dis-use, i.e. when the maximum benefit has been obtained in order to prevent severe toxic manifestations.

In pneumonia it is doubtful whether its immediate exhibition is either necessary, or helpful, as a routine; and each case must be considered on its merits. In all cases good nursing is essential; typing of the sputum advantageous; and, should the progress of the case demand it, the combined use of either the specific or polyvalent immune serum and sulphapyridine should be considered most seriously.

Sulphapyridine has a definite place in the treatment of the dysenteries especially in the sub-acute and chronic stages.

It is to be hoped that the sulphapyridine of to-day will not take the place of the aspirin of yesterday, either as a therapeutic agent, or, as a placebo.

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